Coming of Age: The Legacy of Dolly at 20 Scientific Scientific Symposium

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Scientific Symposium

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Twenty years ago, the first mammal cloned from an adult somatic cell was presented to the world. Dolly the sheep was born from the transfer of a nucleus taken from a mammary gland cell into an unfertilized, enucleated oocyte. This breakthrough, made at the Roslin Institute, University of Edinburgh, had a phenomenal scientific, economic and ethical impact. It provided definitive answers to key questions of the time: Is it possible to change cells from one tissue to another? (Yes) Can a nucleus from a single adult mammalian cell be re-programmed to form an entire new organism? (Yes)

Coming of Age: The legacy of Dolly at 20 celebrations were held in Edinburgh last September 2016. On Thursday the 1st September 2016 the charismatic scientific communicator and author, Dr Kat Arney, hosted a public lecture. Professor Sir Ian Wilmut (University of Edinburgh), Professor Angelika Schnieke (Technical University Munich, Germany) and Professor Shinya Yamanaka (Kyoto University, Japan) introduced to visitors who Dolly was and the impact this research had on future studies. After the three talks, members of the public could quiz the speakers and local researchers on what work they are currently pursuing in the realm of gene editing, developmental biology and regenerative medicine.

This event was followed by a scientific symposium held in the Roslin Institute on Friday the 2nd September, which was jointly organised by the University of Edinburgh's MRC Scottish Centre for Regenerative Medicine and the Roslin Institute. With over 260 scientists from around the world in attendance, including 30 undergraduate students sponsored by the Genetics Society, the impressive auditorium of the Roslin

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Institute was not large enough to contain all the delegates. To accommodate everybody, the event was streamed live into an overflow seminar room and lecture hall and to the Centre for Tropical Livestock Genetics and Health (CTLGH), a partner institution of the Roslin Institute in Nairobi, Kenya.

Professor Sir Ian Wilmut opened the symposium giving a detailed view of the historical events that led to Dolly's cloning. He highlighted previous critical breakthroughs in understanding, from August Weismann's first concept of the continuity of germ-plasm as the basis of heredity to Hans Spemann's famous cleavage experiments of salamander eggs in which he used his daughter's baby hair to demonstrate that the nucleus is critical for embryonic development. In the experiments that led later to the generation of Dolly, Professor Sir Ian Wilmut explained the crucial impact of the cell cycle stage of both the donor and the acceptor cell in determining the efficiency of nuclear transfers.

Cloning or somatic cell nuclear transfer (SCNT) remains the method of choice to genetically engineer livestock, but we also heard of the technical advances in genetic engineering in livestock which is allowing direct editing of the animals without the need for cloning. The recent technology revolution in using genome editing nucleases has allowed to microinject these reagents directly into 1-cell embryos or zygotes to generate defined genetic alterations and thereby to circumvent cloning. Several speakers presented their work on livestock engineering. Cows have been engineered to produce milk with higher casein levels (better for cheese production) or undetectable β-lactoglobulin levels (which can cause milk allergy in infants, presented by Prof Goetz Laible, AgResearch, New Zealand) while chicken 'bioreactors' have been produced that express high levels of HER-2 antibodies in their eggs (Dr Lisa Herron, The Roslin Institute) for the treatment of breast cancers. The production of better large animal models for multiple human diseases is driving much of the translational biomedical research at Roslin and other institutions all over the world. Examples on how livestock genome editing can be used to generate pigs that are resistant to infectious agents (African Swine Fever virus, presented by Dr Chris Proudfoot) or to model different types of human cancer in pigs have illustrated the power of these new emerging technologies. A prime example how such models can advance our understanding of mechanisms underlying cancer development in humans was the targeting of the porcine Adenomatous polyposis coli (APC) gene which produced a faithful model of human colorectal cancer (presented by Prof Angelika Schnieke, Technical University of Munich).

During lunch, delegates were treated to poster presentations from emerging researchers in a foyer packed with energetic debate. There were also a number of stands from the symposium sponsors lining the hall. After lunch, focus switched from livestock genetic engineering to regenerative medicine with research involving murine models and preclinical studies in humans. Nobel Prize Laureate for Medicine or Physiology 2012, Professor Shinya Yamanaka detailed the impact Dolly had in inspiring the generation of induced pluripotent stem (iPS) cells. The fact that Dolly was cloned from a fully differentiated adult mammary cell nucleus was the first indication to the scientific world that reversion of differentiated cells to a pluripotent stem cell like state was indeed possible.

The session that followed provided mechanistic insights into the process of reversing differentiation and the applications of this research. The current estimated cost of applying personalised medicine led several speakers to argue in favour of the creation of iPS libraries from healthy volunteers. Such iPS cells can be rigorously quality controlled and HLA matched for their therapeutic use in recipients

to avoid rejections of transplanted iPS cells by the immune systems. Prof Yamanaka showed that as few as 140 carefully selected iPS cell lines generated from donor peripheral blood or cord blood cells would be HLA compatible with 90% of the Japan population (similar numbers are expected for Britain). How the 'Yamanaka' factors induce pluripotency at the chromatin level was presented by Dr Abdenour Soufi and how cell lineage choices are impacted by morphological changes was presented by Dr Sally Lowell (both MRC Scottish Centre for Regenerative Medicine, University of Edinburgh). A number of speakers also discussed the use of differentiated iPS cells in generating patient derived disease models; an ideal model for testing possible therapeutics.

Prof Marius Wernig (Stanford University, USA) presented his findings how skin derived fibroblasts can be converted into functional neurons. A screen undertaken in his lab has identified three factors critical in reprogramming fibroblast into neuronal cells that can form functional synapses. He has now identified targets of one factor and demonstrated that these orchestrate a repressive regulator program in neurons that suppress other cell lineage identities.

The last session of the symposium focused on the development of therapeutic stem cell approaches for the clinic. Prof Paul Tesar (Case Western Reverse University, Ohio, USA) discussed the role of iPS cells in testing candidate drugs for patients with multiple sclerosis. Prof Stuart Forbes (MRC Scottish Centre for Regenerative Medicine) gave new insights into mechanisms that control liver regeneration after severe injury discussing how impairment of hepatocyte proliferation in these situations might be overcome.

A big overarching theme of this session was the usage of organoids as cell culture models for studying specific mechanisms of disease pathogenesis. Prof Marc van de Wetering (Princess Maxima Center, Utrecht, Netherlands) demonstrated impressively how organoids can be grown from single multipotent stem cells to generate tissue structures that resemble key features of organs.

He discussed how organoid biobanks can be generated from patient biopsies and how these can be used for drug target discovery and therapy development. As an example, he showed how his laboratory is using intestinal organoids derived from colorectal cancer patients to identify drugs that specifically inhibit tumor growth in these patients. Prof Andrew Jackson (MRC Human Genetics Unit, University of Edinburgh) presented in his talk how brain organoids can be used to study mechanisms of microcephaly development.

The organoids his laboratory is growing recapitulate early cortical brain development and can be used to dissect and to understand effects of gene mutations that are associated with inheritable forms of microcephaly.

Ethical discussions where pervasive throughout the whole symposium. Although legislation may not be somewhat behind the latest technologies of iPS cells and genetic editing, the potential for agricultural and medical application is overwhelmingly clear. Will cloning soon be part of the solutions to the ageing population and sustainable food supply in times of global population growth, diet changes and global warming? We are looking forward to answering that question at the Legacy of Dolly at 40 celebrations.

The video recordings of Coming of Age: The Legacy of Dolly at 20 Scientific Symposium talks and the slide show of this event can be found on the following website: https://media.ed.ac.uk/channel/Dolly+at+20+Scientific+Symposium/